Objection to the Specification

The Examiner objected to the specification because the Brief Description of the Drawings fails to describe Figures 3A-3X. The brief description of Figures 3A-3Z and 3A1-3D1 has been amended to clarify that the description pertains to all these figures. Applicants acknowledge receipt of the Notice of Draftsperson's Patent Drawing Review, and will submit formal drawings in compliance with the Draftsperson's remarks if the application is allowed.

The Examiner has also objected to the specification because the abstract has multiple titles. The objected additional title of the application has been deleted from the abstract section.

Applicants have amended the specification to correct these errors, and have thereby obviated this objection.

Rejection of Claims under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 5-7, 9, 11, 13, 14-15, and 17 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The Examiner states that Claims 11 and 13 are essentially duplicates of Claim 5, and Claims 14, 15 and 17 are essentially duplicates of Claims 6, 7, and 9, respectively.

Applicants respectfully disagree. Two independent claims exist: 1 and 11. Claim 1 describes the process of "clustering" the datapoints using a self organizing map (SOM), whereas claim 11 refers to "grouping" the datapoints.

The MPEP, section 706.03(k), states:

> Inasmuch as a patent is supposed to be limited to only one invention, or, at most, several closely related indivisible inventions, limiting an application to a single claim, or a single claim to each of the related inventions might appear to be logical as well as convenient. However, court decisions have confirmed applicant's right to *restate (i.e., by plural claiming) the invention* in a reasonable number of ways. Indeed, a mere difference in scope between claims has been held to be enough. *(Emphasis added)*

In accordance with this passage and the requirements of 35 U.S.C. §112, second paragraph, Applicants have chosen to restate the invention in these two ways. Hence, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claims under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-18 under 35 U.S.C. § 103(a) as being unpatentable over Eisen *et al.*, (Reference AU4 of Form 1449 filed on July 14, 2000; hereinafter "Eisen"); in view of Mangiameli *et al.*, *Eupr J. Operational Res.* 93, 402-417 (1996) (hereinafter ("Mangiameli"); and Kohonen (Reference AR of Form 1449 filed on July 14, 2000; hereinafter "Kohonen"). The Examiner states that Eisen discloses methods of cluster analysis and display of genome-wide expression patterns of genes using hierarchical clustering which comprise the steps of receiving gene expression values of datapoints, clustering the datapoints and providing output display indicating the clusters of the datapoints. The Examiner also states that Mangiameli applied Self Organizing Maps (SOMs) and seven hierarchical methods to 252 messy data sets with real-world data imperfections and found that SOMs is significantly superior in both robustness and accuracy to other clustering methods, thus motivating using SOMs in place of hierarchical clustering analysis. The Examiner further indicates that Kohonen teaches every aspect of SOMs including mathematical preliminaries, justification of neural modeling, etc. Office Action, pages 5-6.

Applicants respectfully disagree. Eisen describes hierarchical clustering in which the relationships among the genes are represented by a tree whose branch lengths reflect the degree of similarity between the objects, as assessed by pairwise similarity function. In sequence comparison, these methods are used to infer evolutionary history of sequences being compared. Eisen goes on to say:

> whereas no such underlying tree exists for expression patterns of genes, degrees of similarity and more distant relationships among groups of closely related genes, as well as requiring few assumptions about the nature of the data. The computed trees can be used to order genes in the original data table, so that genes or groups of genes with similar expression patterns are adjacent. Eisen, at 14863, 2nd collum, last paragraph.

Thus, Eisen describes the use of hierarchical clustering for gene expression data and the passage of Eisen cited in the Office Action, when read in context with the whole paragraph, speaks to the generality of the approach, i.e., that the overall approach is not specific to gene-expression data. The passage states that Eisen has found that a general approach (i.e., viewing complex datasets by first scanning and surveying the large-scale features and then focusing in on the interesting details) can be applied to genomic datasets. Eisen thus concludes "[it] is ...likely that **very**

similar approaches may be applied to many **other kinds** of very large datasets." (Emphasis added). Esien, at 14867, second column. It is noted that in this context the term "many other kinds" refers to datasets other than gene-expression data. The passage goes on to say that "...it may be necessary to find alternative algorithms and computation methods to bring out inherent structures in the data, and equally important to find dense naturalistic visual representations that convey the quantitative information effectively." Id. Again, this statement is inclusive of general large datasets and is not specific to gene-expression data. The subject paragraph lastly states that Eisen is actively exploring alternatives and mentions supervised clustering methods with respect to gene-expression data. However, nowhere does Eisen suggest or imply SOMs clustering in particular for use in analyzing gene-expression data.

In fact, when read as a consistent whole, Eisen teaches away from using a clustering methods such as SOMs. In hierarchical clustering, datapoints are forced into a strict hierarchy of nested subsets so that the closest pair of points is grouped and replaced by a single point representing their set average, and the next closest pair of points is treated similarly, and so on. As described by Eisen, the datapoints are thus fashioned into a phylogenetic tree, whose branch lengths represent the degree of similarity between the sets.

Hierarchical clustering, however, has a number of shortcomings for the study of gene expression. As stated specifically by Eisen, strict phylogenetic trees are best suited to situations of true hierarchical descent, such as in the evolution, of species. Applicants have found and disclose that hierarchical clustering, however, is not well designed to reflect the multiple distinct ways in which expression patterns can be similar. This problem is exacerbated as the size and complexity of the dataset grows. Hierarchical clustering suffers from lack of robustness, non-uniqueness and inversion problems that complicate interpretation of the hierarchy. Finally, the deterministic nature of hierarchical clustering can cause points to be grouped based on local decisions, with no opportunity to re-evaluate the clustering. It is known that the resulting trees can lock in accidental features, reflecting idiosyncrasies of the agglomeration rule. Specification, pages 6-7.

On the contrary the claimed invention utilizes SOMs which have a number of features that make them well suited to clustering and analysis of gene expression patterns. In contrast to the rigid structure of hierarchical clustering, SOMs are ideally suited to exploratory data analysis.

SOMs allow one to impose partial structure on the clusters and facilitate easy visualization and interpretation. They have good computational properties, because they are easy to implement, are reasonably fast, and are scalable to large datasets. One of skill in the art would not be motivated to combine the teachings of Eisen with those of Mangiameli and Kohonen because Eisen discloses the use of a hierarchical clustering that imposes a rigid structure, and neither Mangiameli nor Kohonen recognize the applicability of SOMs to gene expression data to impose partial structure on gene-data clusters. Restated, it is Applicant (and not Eisen, Magiameli or Kohonen) who has brought to light that the rigid structure of hierarchical clustering of gene expression data, as in Eisen, is problematic and that the partial structure of SOMs clustering is a more ideal solution that is scalable to large datasets of gene expression data. As a result, the claimed invention is not made obvious by the cited references, and Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a).

<u>Supplement Information Disclosure Statement</u>

The Examiner stated that the following reference cited on Form 1449 filed by Applicants did not provide a publication date: Gordan, A. D., Chapter 1: "Introduction"; Chapter 2:"Measuring Dissimilarity" and Chapter 3:"Cluster Analysis," *In Classification-Methods for the Exploratory Analysis of Multivariate Data*, (NY: Chapman and Hall), pp.1-53 (1981). Applicants are concurrently filing a Supplement Information Disclosure Statement (SIDS) with the reference properly cited. Entry of the SIDS is respectfully requested.

<div align="center">CONCLUSION</div>

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 5, lines 18 through 19 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Figures 3A-3Z and 3A1-3D1 are graphical representations of a SOM utilizing a 6x5 grid of the yeast cell cycle.